CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-165

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 24, 2008
From	Eric Bastings, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22165
Applicant	ProEthic Pharmaceuticals
Date of Submission	28 September 2007
PDUFA Goal Date	October 27, 2008
Proprietary Name / Established (USAN) names	Diclofenac Potassium for Oral Solution [Tradename]
Dosage forms / Strength	Sachet of powder / 50 mg
Proposed Indication(s)	Acute Treatment of Migraine
Recommended:	*Complete response*

1. Introduction

Proethic submitted a 505(b)(2) application for a new, oral, water-soluble powder formulation (sachet) of diclofenac potassium, PRO-513, for the acute treatment of migraine. The established name of the product is "Diclofenac Potassium for Oral Solution". I will use "PRO-513" or Diclofenac Potassium for Oral Solution interchangeably in this document.

The 505 (b)(2) NDA is based upon reference to three approved NDAs for Cataflam (Diclofenac Potassium immediate release tablets, 50 mg ; NDA 20-142), Voltaren (Diclofenac Sodium enteric coated tablets, 25, 50, 75 mg ;NDA 19-241) and Voltaren XR (Diclofenac Sodium Extended Release tablets, 100 mg; NDA 20-254), plus two bioavailability/tolerability studies, and two pivotal efficacy studies.

2. Background

Diclofenac, either in Sodium salt or Potassium salt form, is a non steroidal anti-inflammatory drug with analgesic and antipyretic actions. Both Sodium and Potassium salt forms of diclofenac formulated as tablets (extended and delayed release), solution for ophthalmic drops and topical gel are currently FDA approved.

3. CMC/Device

Dr. Shastri Bhamidipati from ONDQA conducted the CMC review.

Dr. Bhamidipati recommends approval from a CMC perspective. He notes that the proposed drug product is formulated as powder for oral administration after constituting to a solution in water. The drug product will be available in single dose units, 'sachets', of 50 mg of

diclofenac potassium blended with pharmaceutical excipients, mannitol, aspartame, anise and mint flavors, saccharin sodium and potassium bicarbonate.

Dr. Bhamidipati believes that the sponsor adequately evaluated the dissolution of the powder and flowability of the final mix. He notes that drug product stability data for three registration batches packaged in the primary packaging configuration intended for marketing were provided up to 9 months. Based on analysis of the data and supportive data from additional process validation batches with a different foil for packaging, Dr. Bhamidipati recommends 18 month expiration date as proposed by the sponsor.

Finally, Dr. Bhamidipati notes that the office of Compliance has provided an overall acceptable recommendation for the manufacturing facilities.

4. Nonclinical Pharmacology/Toxicology

Dr. D. Charles Thompson conducted the nonclinical pharmacology/toxicology review, and Dr. Lois Freed conducted the supervisory nonclinical pharmacology/toxicology review. In her memorandum, Dr. Freed notes that the literature review conducted by the sponsor is insufficient to write adequate product labeling for this product. Specifically, a number of published studies showing a potential for diclofenac to induce reproductive or developmental toxicity were identified by Dr. Thompson, none of which was provided by the sponsor. Since current labeling for approved diclofenac NDAs state that nonclinical reproductive toxicology studies are negative, I agree with Dr. Freed and Dr. Thompson that the sponsor should be required to examine the available published nonclinical literature, so that all adverse effects, in particular related to developmental toxicity, are described in labeling.

5. Clinical Pharmacology/Biopharmaceutics

Mrs. Carol Noory performed the clinical pharmacology review. She notes that the sponsor has conducted two bioavailability and tolerability studies. The pivotal study (ProEthics Study PRO513-101) was a single-dose, 4-period crossover trial comparing the relative bioavailability of PRO-513 to Cataflam (diclofenac potassium) tablets under fed and fasting conditions (n=36). A supportive single dose, two-way, crossover study (CAT458C2101) comparing the bioavailability of diclofenac-K sachets to Cataflam tablets was also submitted (n=24). That study was conducted by Novartis.

In study PRO-513101, healthy volunteers received one dose of PRO-513 and one dose of the reference product under fasting conditions, and then received one dose of each treatment under fed conditions (standardized, high-fat, high-calorie meal), with appropriate washout periods. The results of the pivotal study are displayed in Table 1, copied from page 5 of Mrs. Noory's review.

Mrs. Noory noted that under fasted conditions, PRO-513 and Cataflam had a similar AUC, but the Cmax of PRO-513 was 45% higher, and Tmax of PRO-513 was shorter (0.25 h vs. 0.5h)

than that of Cataflam. Under fed conditions, PRO-513 and Cataflam again had a similar AUC, but the Cmax of PRO-513 was 39% than that of Cataflam, and the Tmax of PRO-513 remained shorter than that of Cataflam (0.17h vs. 1.25h).

Table 1: Results of pivotal bioequivalence study PRO-513101

		Geometric LS Means			
Parameter	**Test/Reference**	**Test**	**Reference**	**Geometric Mean ratio* (%)**	**90% Confidence Interval**
FASTED					
AUC0-inf (ng*hr/mL)	A vs B	1203.19	1060.40	113	107.10- 120.21
AUC0-t (ng*hr/mL)		1184.34	1043.87	113	106.86- 120.46
Cmax (ng/mL)		1502.19	1033.32	145	121.12-174.48
FED					
AUC0-inf (ng*hr/mL)	C vs D	1078.28	1035.70	104	98.05- 110.55
AUC0-t (ng*hr/mL)		1025.70	1032.38	99	93.75-105.29
Cmax (ng/mL)		433.22	714.33	61	50.83-72.36
A: PRO-513 (diclofenac potassium) sachet 50 mg fasting					
B: Cataflam® (diclofenac potassium) tablets 50 mg fasting					
C: PRO-513 (diclofenac potassium) sachet 50 mg fed					
D: Cataflam® (diclofenac potassium) tablets 50 mg fed					

Mrs. Noory further comments that study PRO-513101 also showed a marked (72%) reduction of PRO-513's Cmax after a high fat meal compared to fasting, whereas the reduction of AUC was modest (12%). PRO-513's Tmax was also longer after a high fat meal (1.25h vs. 0.5h) than fasting. Mrs. Noory notes that this may result in a reduction in effectiveness if the product is taken immediately after the intake of a high fat meal, but that mild or moderate fat meals are likely to have a decrease in Cmax of a lesser magnitude. She correctly notes that the clinical effectiveness trials were conducted without regard to meals, and that therefore the impact of concomitant meal intake could not be assessed.

Similar findings were observed in supportive Study CAT458C2101. In the fasted state, PRO-513 and Cataflam had a similar AUC, but Cmax of PRO-513 was markedly higher (109%). PRO-513 Tmax was shorter than that of Cataflam (0.25h vs. 0.5h).

The comparative pharmacokinetics between PRO-513 and Cataflam are important, because the sponsor relied on the long-term safety experience with Cataflam to establish safety of PRO-513. Mrs. Noory comments that a typical migraine patient would neither be completely fasted or fed with a high-fat meal at the onset of the migraine, but would be in a state between the two. Moreover, she comments that diclofenac potassium is approved for the treatment of dysmenorrheal and mild to moderate pain at doses up to 150 mg. Mrs. Noory believes that the 45-109% increase in Cmax noted for PRO-513 50mg, would likely fall within the range of Cmax seen with a 100 mg dose of Cataflam, given the inter-subject variability of 30-60% for Cmax noted in the PK studies. I agree, and so does Dr. Farkas, who believes that based on these pharmacokinetic data and comparable patient population, reliance on past safety experience is acceptable (see below).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Julia Luan conducted the statistical review, and Dr. Ron Farkas conducted the clinical review.

Dr. Luan notes that this NDA submission includes two pivotal efficacy studies, Study PRO-513301 and CAT458C2301.

Study PRO-513301 was a Phase III, randomized, double-blind, parallel group, single-dose, placebo-controlled, multi-center study to compare the efficacy and safety of PRO-513 to placebo as a treatment for migraine attacks in adult subjects. This study was conducted in 23 US sites. The ITT population included 690 subjects. During the course of the study, enrolled subjects treated one eligible migraine attack (with or without aura) that presented with at least moderate headache pain intensity. Using a diary, subjects assessed their headache pain and other associated symptoms (nausea, photophobia, phonophobia, presence or absence of vomiting, and functional ability with regard to daily activities) just prior to dosing, and then at 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, 8, 16, and 24 hours after dosing.

Study CAT458C2301 was a double-blind, double-dummy, randomized, multi-center, cross-over trial to assess the efficacy and tolerability of single doses of 50 mg diclofenac-K sachets as an acute treatment for migraine attacks in comparison with placebo and 50 mg diclofenac-K tablets in adult migraine patients. This study was conducted in Europe. Subjects were to treat three migraine attacks over a two-month period. The three treatment sequences were diclofenac-K sachets/diclofenac-K tablet/placebo, diclofenac-K tablets/placebo/diclofenac-K sachets, placebo/diclofenac-K sachets/diclofenac-K tablets. Out of the 328 patients randomized, 317 received at least one treatment and 274 treated all three migraine attacks with study drug.

I created Table 2 from the study results as analyzed by Dr. Luan.

Table 2: Summary of efficacy results of pivotal studies

	PRO-513	Placebo	p
Study PRO-513301			
Pain-free	25%	10%	<0.002*
Nausea-free	65%	53%	
Photophobia-free	41%	27%	
Phonophobia-free	44%	27%	
Study CAT458C2301			
Pain-free	25%	12%	<0.0001
Nausea-free	66%	54%	0.055
Photophobia-free	59%	49%	0.042
Phonophobia-free	65%	52%	0.007

*Sponsor and FDA analysis
^ FDA analysis

With the exception of a borderline p value for nausea-free in Study CAT458C2301, all results were statistically and clinically significant.

Dr. Luan confirmed the sponsor's analyses for Study PRO-513301.

For Study CAT458C2301, Dr. Luan conducted a McNemar's test for each of the three sequences to compare diclofenac sachet and placebo. Dr. Luan notes that since for each of the three McNemar's tests the test statistic has a distribution and the three test statistics are independent, the sum of the three test statistics has a distribution, which could be considered as an overall test. The p values presented in Table 2 reflect that analysis. Because of a 14% dropout in the study, Dr. Luan also conducted a first period analysis, which generally confirmed the study results (3 out of 4 key efficacy endpoints statistically significant).

It is important to note that Study CAT458C2301 allowed patients to treat their migraine when the pain was mild, moderate, or severe. Our typical requirement is that the drug be showed to be effective on migraine attacks with moderate or severe pain. However, only a small proportion of patients (<10%) treated their headache when the pain was of mild intensity, and the pain-free rate in the subpopulation of patients with baseline pain of moderate or severe intensity was also robustly superior on drug vs. placebo (24% vs. 13%, p<0.0001).

Dr. Farkas essentially agrees with Dr. Luan.

8. Safety

Dr. Farkas conducted the safety review. Dr. Farkas finds PRO-513 acceptably safe in acute migraine based on previous FDA findings of safety for diclofenac tablets, combined with additional safety data in the studies submitted in this NDA.

Dr. Farkas notes that FDA previously found diclofenac tablets safe in populations and indications similar to migraine. In particular, the primary dysmenorrhea population is similar in age and gender to the migraine population, and uses diclofenac on a similar chronic intermittent schedule. Dr. Farkas also notes that diclofenac is also approved for 'pain' which would encompass a broad population inclusive of patients similar to the migraine population that in some circumstances use the drug on a chronic intermittent schedule.

In addition, Dr. Farkas notes that diclofenac exposure from PRO-513 is similar to that from a single 50 mg diclofenac tablet, and is likely always less than the exposure from two 50 mg diclofenac tablets, a higher dose that is also approved for primary dysmenorrhea and pain.

I agree, and also refer the reader to the OCP review and to the discussion of the pharmacokinetic studies results above.

Dr. Farkas also reviewed safety data from the new bioavailability and efficacy studies submitted with this NDA, in which about 600 migraine patients were exposed to a single dose of PRO-513, 50 healthy volunteers were exposed to 2-4 doses of PRO-513, and 74 patients with dental pain were exposed to a single dose of PRO-513. Dr. Farkas observed some limitations in the data collection methodology in the European migraine and in the dental pain study, but observes that overall the new adverse events data provided by the above studies did not raise significant new safety concerns about PRO-513.

9. Advisory Committee Meeting

No advisory meeting is needed. There are already a vast experience with a number of NSAIDs approved for various indications, including migraine, and this 505(b)(2) is for diclofenac, which is not a new molecular entity.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. I recommend that this drug be studied in adolescent migraine patients age 12-17. If safety and efficacy is demonstrated in that age group, the sponsor should be required to study pediatric migraine patients 6-11. I recommend a waiver for patients age 0-5, because the necessary studies are impossible or highly impracticable (migraine is difficult to diagnose in children under age 6 years and the critical design elements for adequate studies in this age group for this drug are unknown).

11. Other Relevant Regulatory Issues

A DSI inspection was conducted on 2 sites (Dr. Saper, and Dr. Tomasovic). No significant deficiency was identified.

12. Labeling

The sponsor submitted the trade name, Cambia, for the drug product in their amendment (dated 22-JUL-2008) which is pending review by the Division of Medication Error Prevention and Analysis (DMEPA).

Labeling will be negotiated during the next cycle. The sponsor did not send labeling in the proper format with the application, but corrected the format in a late submission to the NDA.

A Medication Guide will be required, because the product is a NSAID. Therefore, a REMS will be requested to the sponsor in the action letter.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: I recommend a complete response action. The non clinical issue described above must be addressed prior to approval. A REMS must also be submitted by the sponsor (see below).

Risk Benefit Assessment: Safety and efficacy of the product have been established. Safety is essentially based on prior approval of diclofenac for similar patient populations. Efficacy was established in two new pivotal efficacy studies, in which the product was clearly superior to placebo for the key efficacy endpoints of pain, nausea, photophobia, and phonophobia.

Recommendation for Postmarketing Risk Management Activities: a REMS is required, as the product is an NSAID, and FDA requires Medication Guides for all NSAIDs.

Recommendation for other Postmarketing Study Commitments: None.

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/s/

Eric Bastings
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MEDICAL OFFICER